Glucolipotoxicity, β-Cells, and Diabetes: The Emperor Has No Clothes

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Reduction of β-cell mass and function is central to the pathogenesis of type 2 diabetes. The terms glucotoxicity, lipotoxicity, and glucolipotoxicity are used to describe potentially responsible processes. The premise is that chronically elevated glucose levels are toxic to β-cells, that elevated lipid levels in the form of circulating free fatty acids (FFA) also have toxic effects, and that the combination of the two, glucolipotoxicity, is particularly harmful. Much work has shown that high concentrations of FFA can be very damaging to β-cells when used for in vitro experiments, and when infused in large amounts in humans and rodents they produce suppression of insulin secretion. The purpose of this Perspective is to raise doubts about whether the FFA levels found in real-life situations are ever high enough to cause problems. Evidence supporting the importance of glucotoxicity is strong because there is such a tight correlation between defective insulin secretion and rising glucose levels. However, there is virtually no convincing evidence that the alterations in FFA levels occurring during progression to diabetes are pathogenic. Thus, the terms lipotoxicity and glucolipotoxicity should be used with great caution, if at all, because evidence supporting their importance has not yet emerged.

As described in Wikipedia: "'The Emperor's New Clothes'…is a short tale written by Danish author Hans Christian Andersen, about two weavers who promise an emperor a new suit of clothes that they say is invisible to those who are unfit for their positions, stupid, or incompetent—while in reality, they make no clothes at all, making *everyone* believe the clothes are invisible to them. When the emperor parades before his subjects in his new 'clothes,' no one dares to say that they do not see any suit of clothes on him for fear that they will be seen as stupid. Finally, a child cries out, 'But he isn't wearing anything at all!'" (1).

MY DOUBTS ABOUT GLUCOLIPOTOXICITY BEING A REAL PROBLEM FOR β-CELLS IN DIABETES

How often have we heard talks about type 2 diabetes (T2D) in which a speaker without hesitation has stated that pancreatic β-cells are damaged by "glucolipotoxicity"? At times I have raised my hand to ask if there were data to substantiate such a phenomenon, but my concerns have usually been brushed aside. The popularity of the concept seems to have even intensified over the past decade, which leads me to raise my hand more forcefully to ask: Where are the data that support the concept that glucolipotoxicity contributes to the β-cell failure of T2D? At present my view is that the phenomenon glucose toxicity (glucotoxicity) is real and important for β-cells, while lipotoxicity and glucolipotoxicity, as the terms are now used, have not yet been shown to be a real-life problem. I continue to wait for data that will change my mind.

HOW THE GLUCOLIPOTOXICITY STORY DEVELOPED

Because T2D is such an important health problem and because β-cell dysfunction is a fundamental part of its pathogenesis, enormous effort has been devoted to finding out what has gone wrong (2–4). There should now be agreement that in T2D there is a reduction in β-cell mass and function that is unable to compensate for whatever insulin resistance is present. As β-cell mass becomes inadequate and glucose levels rise, β-cell function becomes impaired. Thus, with full-blown T2D, β-cell mass is typically 40–60% of normal (5,6) and, to make matters worse, the remaining β-cells are functioning at perhaps as little as only half their capacity (7).

Interest in the potential importance of lipids in the pathogenesis of diabetes received a boost from a provocative article from Dennis McGarry in 1992 entitled "What if Minkowski had been ageusic? An alternative angle on

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diabetes" (8). The argument was that the lipid changes occurring in diabetes had been largely ignored. This was followed by a number of studies arguing that lipids have a toxic effect on β-cells. Roger Unger postulated that accumulations of triglycerides in the islets of Zucker Diabetic Fatty (ZDF) rats, a model of T2D, were toxic (9,10). There was early focus on the concept that free fatty acids (FFA) were likely to be the offending agents (11,12). The thinking was that T2D was associated with high FFA levels and that these exerted toxic effects upon β-cells in part related to triglyceride accumulation. For many years, the focus of a large amount of work was on what was called lipotoxicity, and then in 2002 the term glucolipotoxicity was introduced with the argument that high levels of glucose and FFA work synergistically to damage β-cells (13).

ARE THERE CORRELATIONS BETWEEN FFA LEVELS AND β-CELL DYSFUNCTION IN HUMANS DURING THE PROGRESSION FROM THE NONDIABETIC STATE TO T2D?

As will be discussed later, there are very tight correlations between rising glucose levels and dysfunctional insulin secretion justifying use of the term glucotoxicity. As individuals progress to the state of impaired glucose tolerance and then onto diabetes, there is a very good correlation between glucose levels and the loss of first-phase glucose-induced insulin secretion (GSIS) (14,15). However, it has been difficult to find clear correlations between β-cell dysfunction and FFA, or other types of circulating lipids. We know that obese individuals without diabetes have high rates of insulin secretion (16,17) that compensate for insulin resistance. However, as they progress to diabetes, their first-phase GSIS deteriorates in lockstep with rising glucose levels (14), while their FFA levels change very little if at all (18,19). High FFA levels are considered to be a risk factor for the development of T2D (20); this makes sense because they are associated with and even contribute to insulin resistance, which places secretory demands on β-cells (21,22). Thus, elevated FFA can contribute to the pathogenesis of T2D through their effects on insulin action, and probably not through direct toxic effects on β-cells.

WHY GLUCOTOXICITY IS REAL AND IMPORTANT

As stated, there is a very tight correlation between loss of first-phase GSIS and rising glucose levels in humans (14,15). This is most clearly seen as individuals progress from normal glucose tolerance to T2D but is also seen when first-phase GSIS is lost in the progression to type 1 diabetes (23). This failure of β-cells to respond well to a glucose challenge also occurs when islets are cultured in media containing high glucose concentrations (24). We also know that exposure of β-cells to high glucose levels leads to marked changes in gene expression, which is called by many dedifferentiation (25). With such a disruption of the β-cell machinery, it is not surprising that this would lead to reduced insulin output for any given mass of β-cells when hyperglycemia is present. Importantly, these secretory abnormalities can be reversed when glucose levels are returned to the normal range, as has been well shown when T2D is reversed by gastric bypass surgery (26), which provides a strong rational for aggressive glucose-lowering treatments for diabetes (27).

Although it seems reasonable to accept the relationship between high glucose levels and impaired secretory function, we do not have a good understanding of the responsible molecular mechanisms or of how hyperglycemia influences β-cell birth and death, in spite of a huge amount of work. We think it likely that glucose-induced overwork and toxicity increase the rate of β-cell death, which results in decreased β-cell mass, but we do not know this for certain.

WHAT DO WE LEARN FROM THE ADDITION OF FFA TO ISLET CELLS IN VITRO?

There is an extensive literature on the toxic effects of FFA on β-cells in vitro. The most widely used FFA is palmitate, and we know that certain concentrations are toxic to β-cells, causing functional changes, phenotypic changes, and even death. A complicated question is: what are the lipid concentrations that β-cells actually see in vivo? Although palmitate is commonly used, in real-life cells are exposed to a mixture of fatty acids, which are of varying length and saturation. We can only speculate about the concentrations of any fatty acid in the interstitial space surrounding the lipid bilayer plasma membrane of cells. We know that FFA are mostly bound to albumin (28) and that the concentrations of the unbound fatty acids in that space are not known. In a large cohort of subjects, mean ± SD FFA levels were 574 ± 230 mmol/L in nonobese subjects and 714 ± 230 in obese subjects (29). Moreover, we still do not have a good understanding of how FFA are taken up by cells. A potential complication with the use of palmitate is that it may be converted to the potentially toxic compound tripalmitin, which seems not to be a problem in vivo but could be with in vitro studies (30). The point of this discussion is that we cannot assume that the concentrations measured in the circulation are those adjacent to the β-cell membrane, which makes it difficult to understand the relevance of these in vitro experiments.

IS TRIGLYCERIDE ACCUMULATION IN β-CELLS A PROBLEM?

Early thinking about lipotoxicity focused on lipid accumulation in β-cells, and the Unger laboratory reported that islets from ZDF rats with late-stage severe diabetes contained high concentrations of triglycerides (10). This immediately raised questions about whether these lipid stores were toxic, but one must also ask whether these lipid deposits were actually contained in β-cells. We know that fibrosis can be found in islets of late-stage ZDF rats, which raises the possibility that the lipid was contained in nonislet cells. Indeed, we have not found studies that

looked for lipid droplets in these β-cells. In our rat partial pancreatectomy model, which we consider to have glucotoxicity of β-cells, we were unable to find increased levels of circulating FFA or high concentrations of triglycerides in islets (31). There are lipid-containing particles in β-cells called lipofuscin bodies, which are not lipid droplets, but they accumulate in human β-cells over time and do not seem to be related in the presence of diabetes (32).

WHAT CAN WE CONCLUDE FROM THE INFUSION OF LIPIDS INTO HUMANS AND ANIMALS?

There have been a large number of studies in which lipids have been infused into animals and humans looking for an influence on β-cell function, but in almost all, the circulating FFA levels were far higher than normal. An instructive study showed that infusion of Intralipid with heparin into normal subjects raised FFA levels threefold, resulting in an increase in an acute GSIS response at 6 h but a decrease at 24 h (33). Similar results were obtained by Carpentier et al. (34) who showed that lipid infusions caused insulin resistance with early enhanced GSIS but then a loss of this secretory compensation at 48 h. When glucose and lipid were infused for 24 h into normal subjects, impairment of β-cell function could again be demonstrated (35). In contrast to these demonstrations of impaired GSIS, arginine-induced insulin secretion was not altered after lipid was infused for 48 h in obese subjects without diabetes (36). An interesting result emerged from a study by Kashyap et al. (37), which concluded that lipid infusions led to impaired GSIS in subjects without diabetes with a family history of T2D but not those without.

In a study employing rats, infusions of Intralipid plus heparin were given for 48 h and oleate was infused for the same time period as a separate experiment. FFA levels increased to double normal levels, and insulin responses to a hyperglycemia clamp were impaired (38). These results were similar to earlier studies in rats that also examined a 48-h time period (39). Further insights were obtained from a study in *db/db* mice concluding that the loss of β-cell differentiation and secretory function occurred independently of lipid levels, using a strategy of selectively lowering lipid levels with bezafibrate and glucose levels with phlorizin (40).

There is now a consistent body of work showing that long-term infusions of lipid into humans and rats can reduce GSIS, but in all of these studies the FFA levels were far higher than are found in subjects with diabetes. Thus, although FFA levels are higher in diabetes and obesity than in normal weight individuals, we do not have evidence that FFA levels in this range are exerting toxic effects on β-cells.

THE SEARCH CONTINUES TO FIND WAYS IN WHICH LIPIDS CAN BE TOXIC TO β-CELLS

Because we know that exposing β-cells to high concentrations of FFA can lead to impaired secretory function and even death, there has been eagerness by many to leap to the conclusion that they do this in real life and contribute in a major way to the pathogenesis of T2D. While I have voiced my concerns about the interpretation and even relevance of the many studies in which FFA were added to cells in vitro or infused into animals or people, it is entirely possible that lipids in some form exert important toxic effects on β-cells. However, in spite of intensive ongoing investigation, the culprit (or culprits) have not yet been identified. If some type of toxic lipid process is found, the challenge would be in naming it. It would seem inappropriate to use such an imprecise term as lipotoxicity; rather, something more specific like "lipid factor X toxicity" should be used. The term glucotoxicity is justified because of the strong evidence that glucose is causing the problem.

Over the past 20 plus years, a remarkable amount of work has been done to define these mechanisms in the hope that new insights could lead to new therapies (41–44). Many hypotheses have been explored, and we now have a vast amount of descriptive and even mechanistic information about the FFA-induced cellular changes that accompany β-cell secretory dysfunction and death. It must be recognized, however, that much work has been done to identify alterations in lipid metabolism that are harmful to β-cells other than exogenous FFA.

Disruptions of Lipid Metabolism

Questions have been raised about potential disruption of the Randle cycle. This could result from increased oxidation of FFA in β-cells, which would decrease the activity of pyruvate dehydrogenase, thus lowering the rate of glucose oxidation resulting in reduced insulin secretion (45,46). Another concern raised by Prentki and Corkey is the hypothesis of lipid partitioning whereby increased glucose metabolism from hyperglycemia leads to the generation of malonyl-CoA, which via carnitine-palmityl transferase-1 inhibits FFA oxidation leading to the generation of potentially toxic long-chain acyl-CoA esters (12,41). Other lipids meriting attention are the ceramides. These biologically active sphingolipids can be generated by cleavage of plasma membrane lipid sphingomyelin by sphingomyelinases or can be formed de novo from fatty acids such as palmitate or serine (47,48) and have been shown to lead to oxidative stress, mitochondrial dysfunction, and apoptosis. It may turn out that ceramides are playing a key role in the toxic effects of high concentrations of added FFA. Importantly, the toxic effects of glucose alone could be related to or even dependent on changes in ceramides, but this has not yet been shown; even if it were the case, the term "glucolipotoxicity" would not be a good fit.

Oxidative and Endoplasmic Reticulum Stress

The possibility that glucolipotoxicity might damage β-cells through oxidative stress has attracted a great deal of attention (42,44,49). One of the attractions was the finding that β-cells have low concentrations of enzymes that defend against oxidative injury, in particular catalase, superoxide dismutase, and glutathione peroxidase (50).

This vulnerability is demonstrated by the observation that rodent β-cells are killed very easily by the oxidizing toxin streptozocin that is taken up by the glucose transporter Glut2, while hepatocytes, which have the same uptake mechanisms, are resistant. Many of the studies that have examined this oxidative injury have been discussed in a comprehensive review by Poitout and Robertson (42). One of the complicated aspects of this question is the difficulty of sorting out the toxic effects of reactive oxygen species from their effects needed for optimal insulin secretion (41,51). Endoplasmic reticulum stress is another important concern for β-cells because it not only activates the unfolded protein response but, when severe, can induce apoptosis. A recent review discusses work linking lipotoxicity, endoplasmic reticulum stress, and T2D (52). Yet another potential source of trouble that may need a new look is mitochondrial abnormalities (53) and uncoupling. Uncoupling protein-2 (UCP-2) has also been examined as a potential source of toxicity in that some data suggest that FFA may activate UCP-2, which could lead to less ATP production to drive insulin secretion (54,55).

Disruption of Transcriptional Control

Many studies have shown that high levels of FFA can induce changes in transcription factor expression, which can lead to β-cell dysfunction and vulnerability in countless ways. Much of this work has previously been reviewed (42). As an example of areas that need further work, alterations have been found in the expression of SREBP-1c and ChREBP in β-cells exposed to hyperglycemia (56,57), and they have major effects on lipid metabolism. The possibility that these factors are toxic to β-cells needs more study.

In addition, miRNAs could contribute to cellular dysfunction as suggested by a recent article implicating miR-299-5p, which targets the p53 apoptosis effector related to PMP-22 (PERP) (58). However, the link to glucolipotoxicity was inferred from experiments in which palmitate was added to cells in vitro; this is another example of the need to question the relevance of changes induced by the addition of FFA to cells.

Effects of Lipids on β-Cell Turnover

β-Cell turnover in adult humans occurs at a very slow rate but is a key determinant of β-cell mass and therefore a fundamental issue for understanding T2D. A review has pointed out that FFA can either increase or decrease rates of proliferation depending upon the experimental situation (59). Unfortunately, data showing that the FFA concentrations found in obesity and T2D influence β-cell proliferation have not emerged. A few studies have found increased markers of β-cell apoptosis in pancreases obtained from individuals with T2D, but there are unpublished anecdotal reports of failure to confirm this. A very important caveat is that one should not rule out important effects of lipids on β-cell turnover because our current measurement tools are not sensitive enough to show it.

CONCLUSION

We must appreciate the efforts of hundreds of dedicated talented researchers who have worked on the hypothesis that high FFA levels are toxic and therefore make important contributions to the β-cell dysfunction of T2D. They have focused on specific questions with rigorous experiments, but I fear that they have often not asked hard questions about the importance of the path they are taking. The key question that receives insufficient attention is: are the FFA levels seen in real life high enough to damage β-cells? By focusing on this issue, I conclude that we lack convincing correlations between circulating FFA levels and β-cell dysfunction in humans and that high concentrations of FFA added to β-cells in vitro or infused into humans or rodents do indeed have toxic effects. However, we are missing the demonstration that the FFA levels that actually occur in obesity and diabetes are in any way damaging to β-cells. I hope that my challenge of the glucolipotoxicity hypothesis, whether I am right or wrong, is helpful.

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